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GB A 2196251   GB A 2181346

(58) Field of search
A5B
C2C
Selected US specifications from IPC sub-class
A61K

(54) Anti-anxiogenic compositions containing dioxopiperidine derivatives

(57) Phenyl-3-aminoalkyl-4-methyl-2, 6-dioxopiperidines of the Formula I
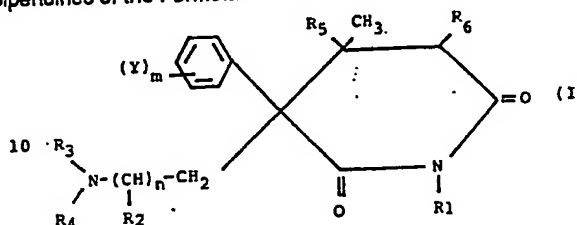
wherein:
R_1 represents hydrogen or C_1–C_4 alkyl;
n is 1 or 2;
R_2 represents hydrogen or methyl, provided that one R_2 is hydrogen when n is 2;
R_3 represents hydrogen or C_1–C_2 alkyl;
R_4 represents C_1–C_2 alkyl;
R_5 and R_6 independently represent hydrogen or methyl;
m is 0 to 3; and
each Y is in a meta or para position and independently represents hydroxy, C_1–C_2 alkoxy, C_1–C_2 alkyl, C_1–C_2 hydroxyalkyl, halogen, or trifluoromethyl, provided that hydroxy and alkoxy are not in the para position, and pharmacologically acceptable salts thereof antagonise anxiogenesis associated with withdrawal from addictive drugs, especially alcohol, cocaine and nicotine.

The presently preferred compound is 3-(3'methoxyphenyl)-3-(3"-N,N-dimethylaminopropyl)-4, 4-dimethyl-2, 6-dioxopiperidine (AGN 2979).

GB 2 206 491 A

The drawing(s) originally filed was (were) informal and the print here reproduced is taken from a later filed formal copy.
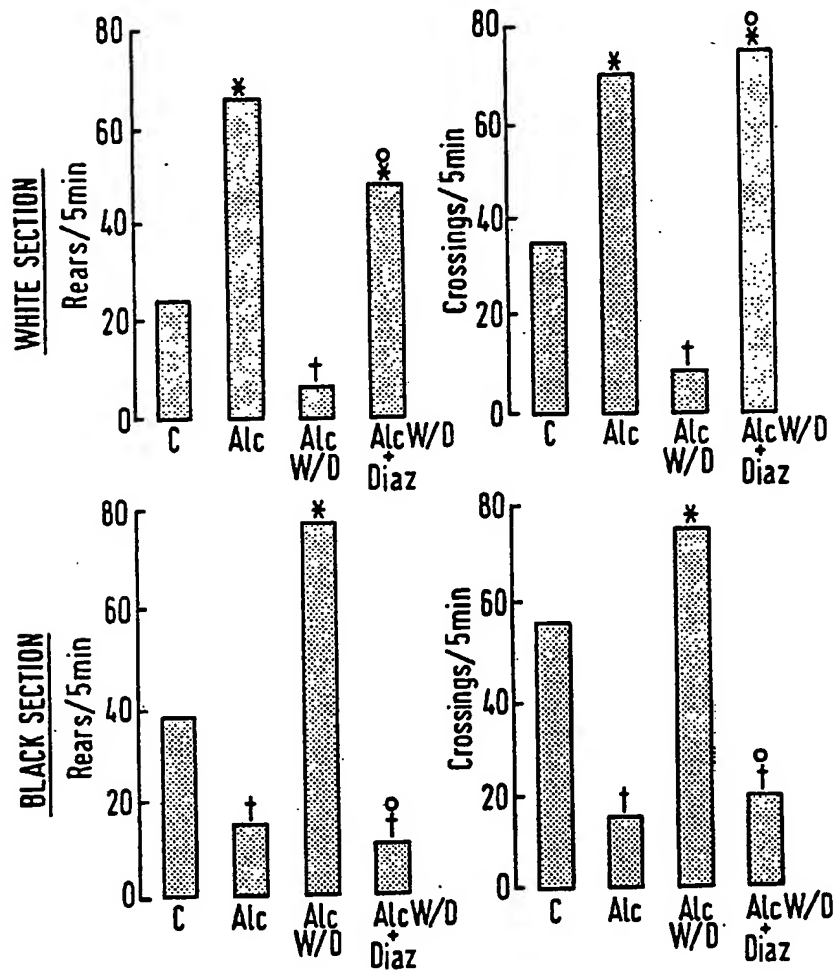
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FIG. 1.

Antagonism of withdrawal anxiogenesis [8% w/v, for 14 days, 48h W/D]
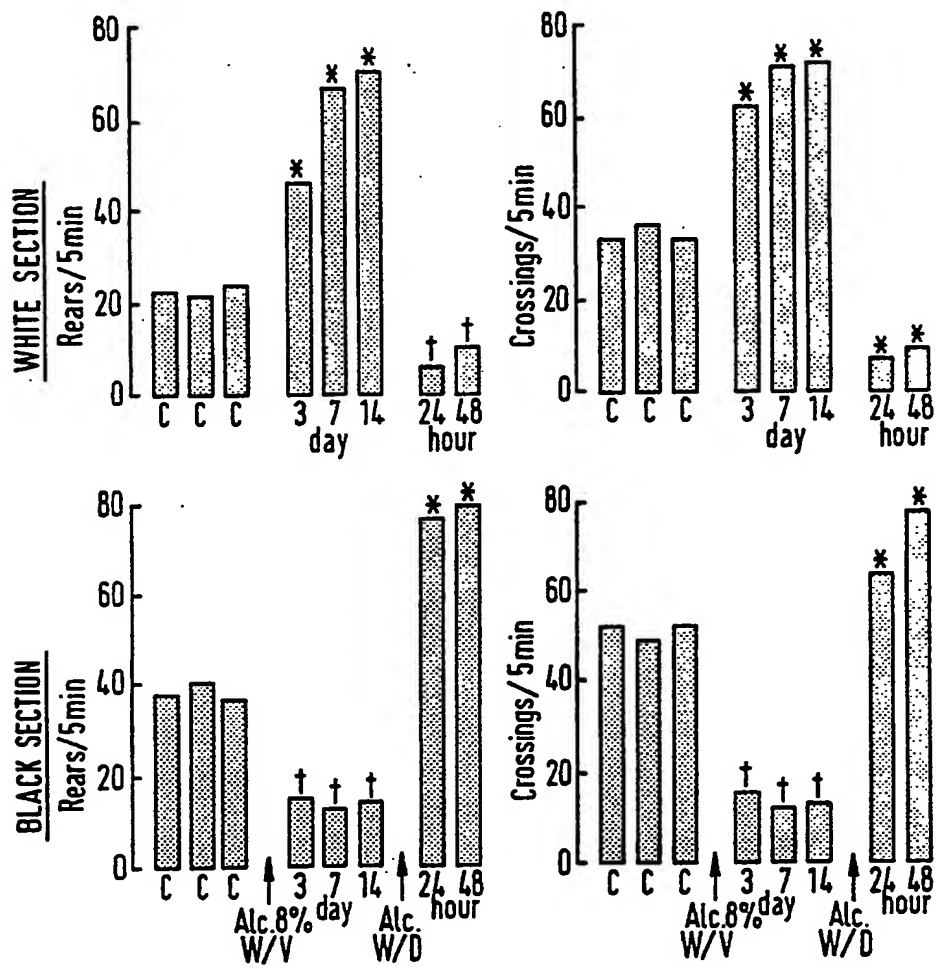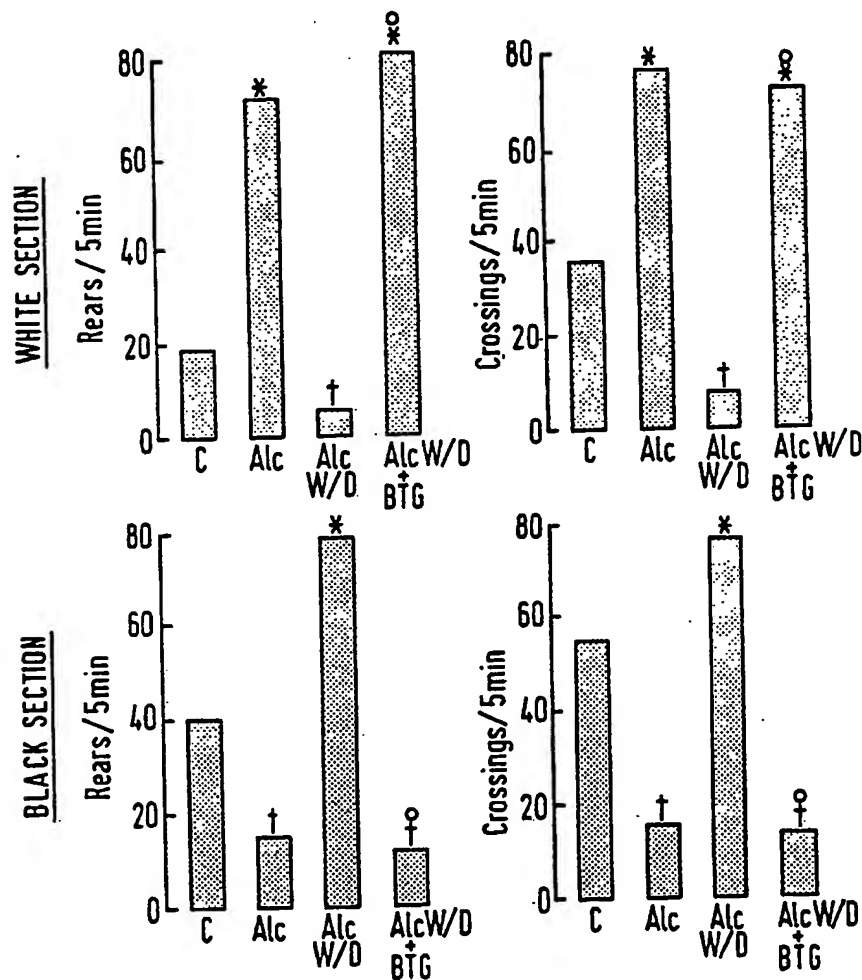by diazepam [10mg/kg i.p.]

2206491

FIG. 2.

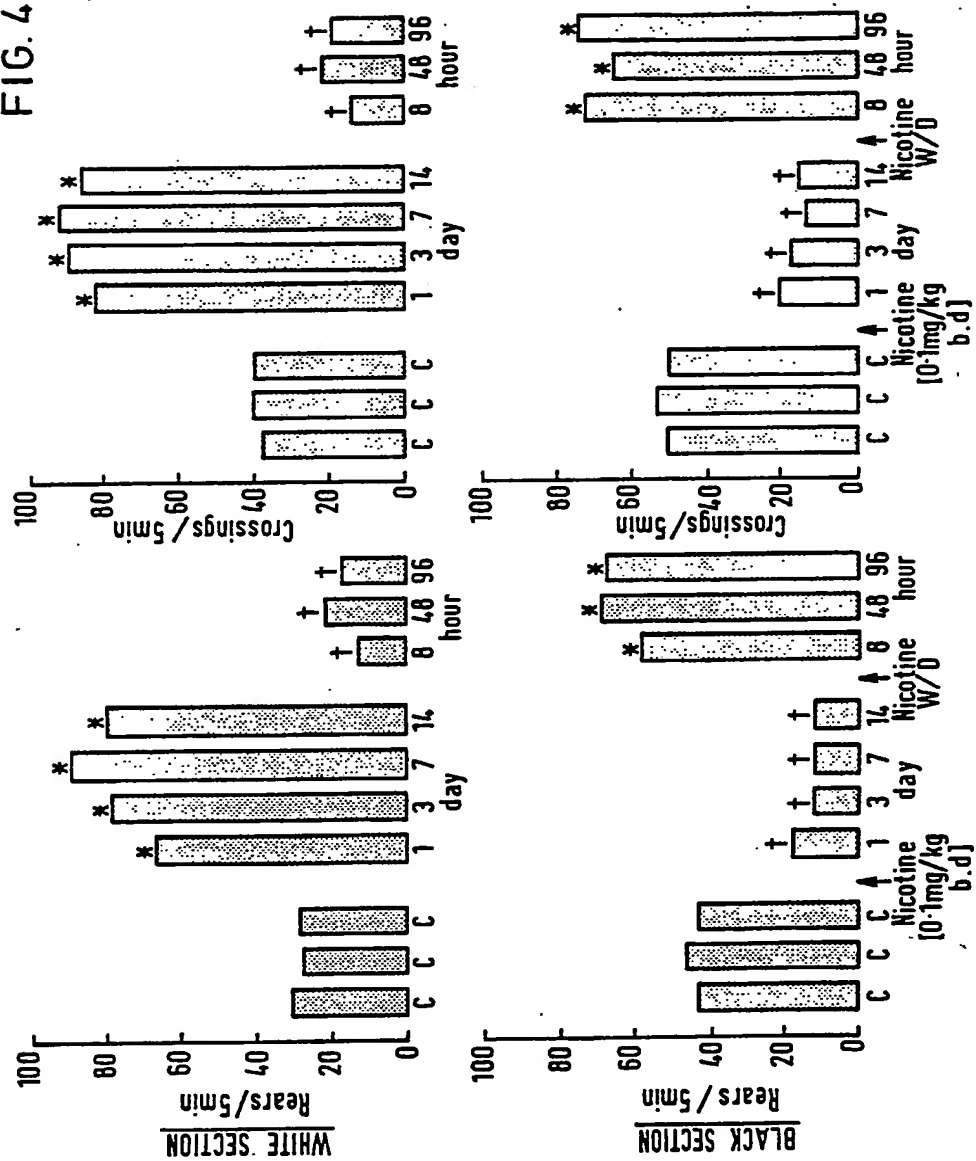Anxiolytic action of alcohol and anxiogenesis following its abrupt withdrawal

FIG. 3.

Antagonisom of alcohol withdrawal anxiogenesis [8%w/v,14days, 48h W/D]
by BTG 1501 [0·5mg/kg i.p.].

FIG. 4.

FIG. 5.

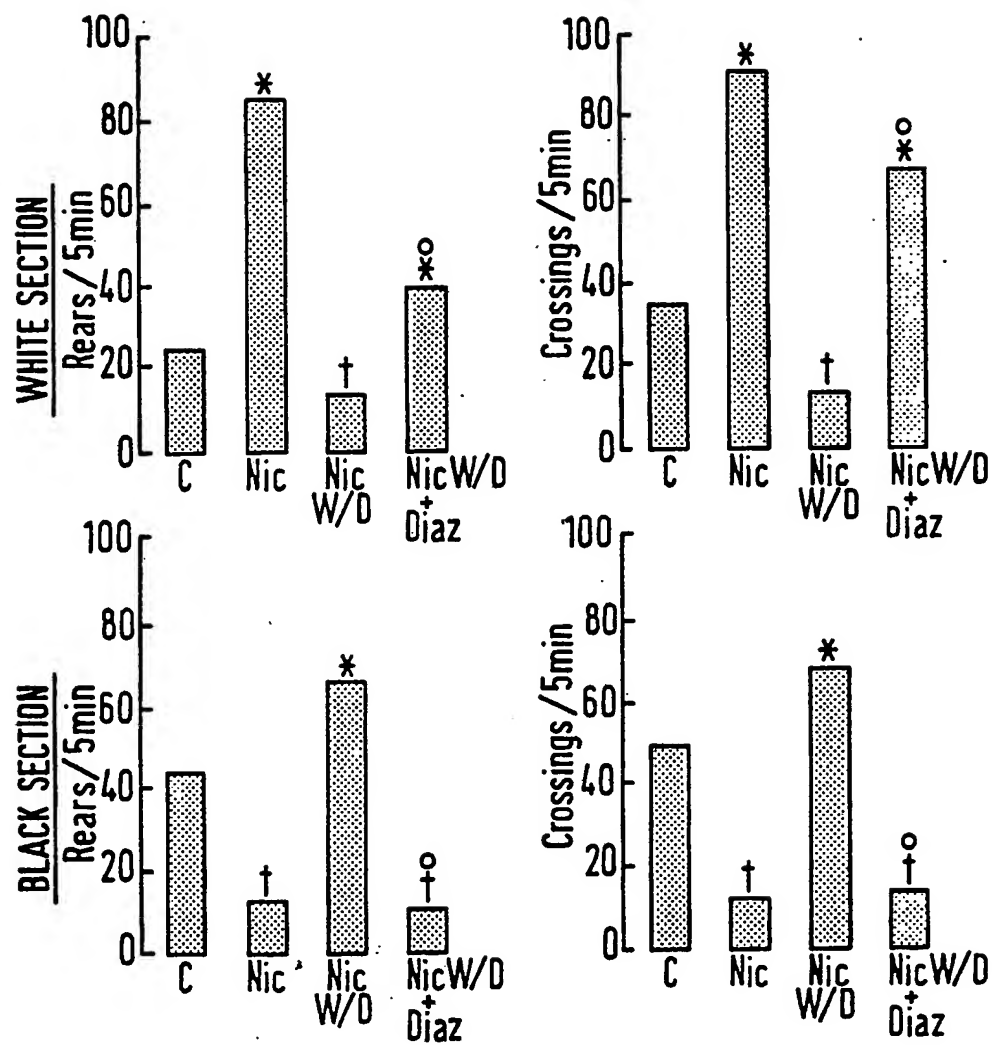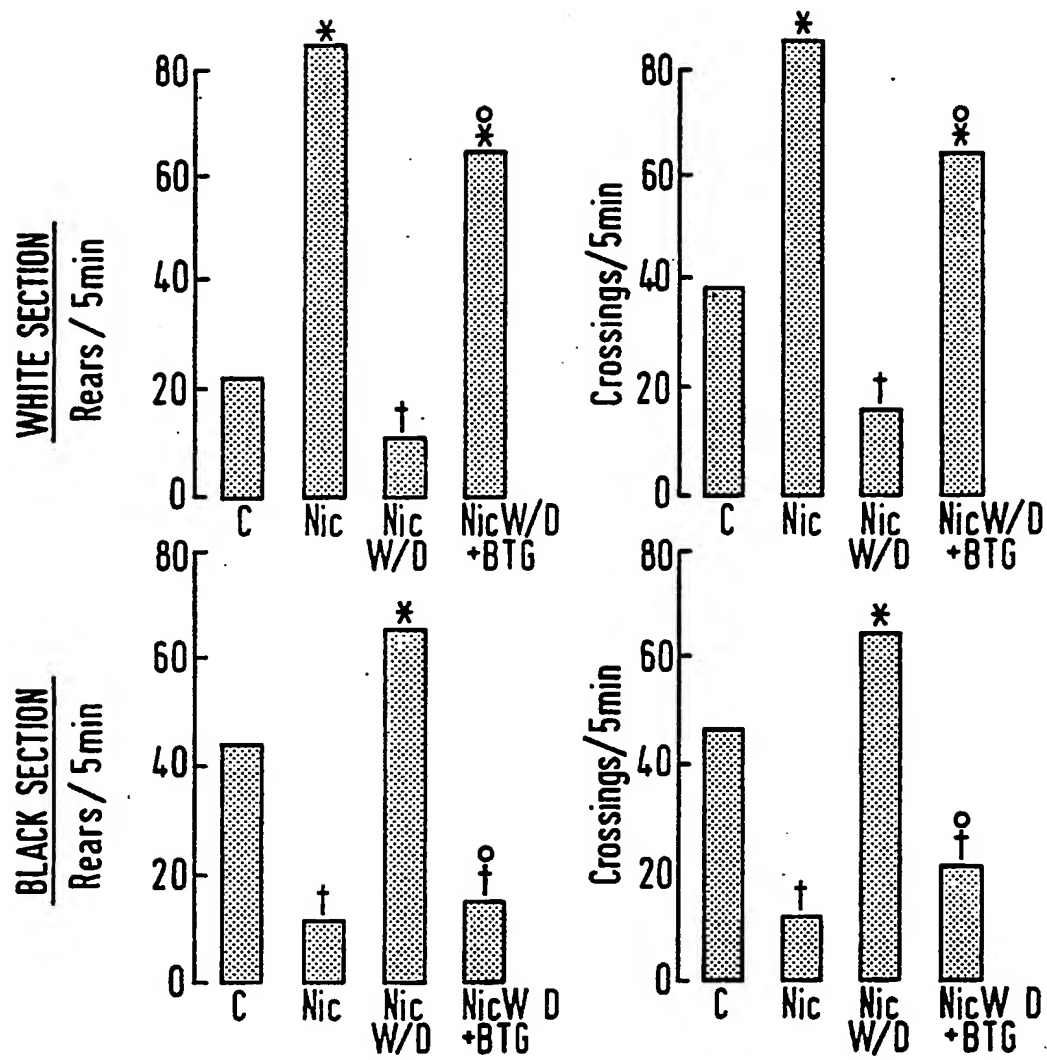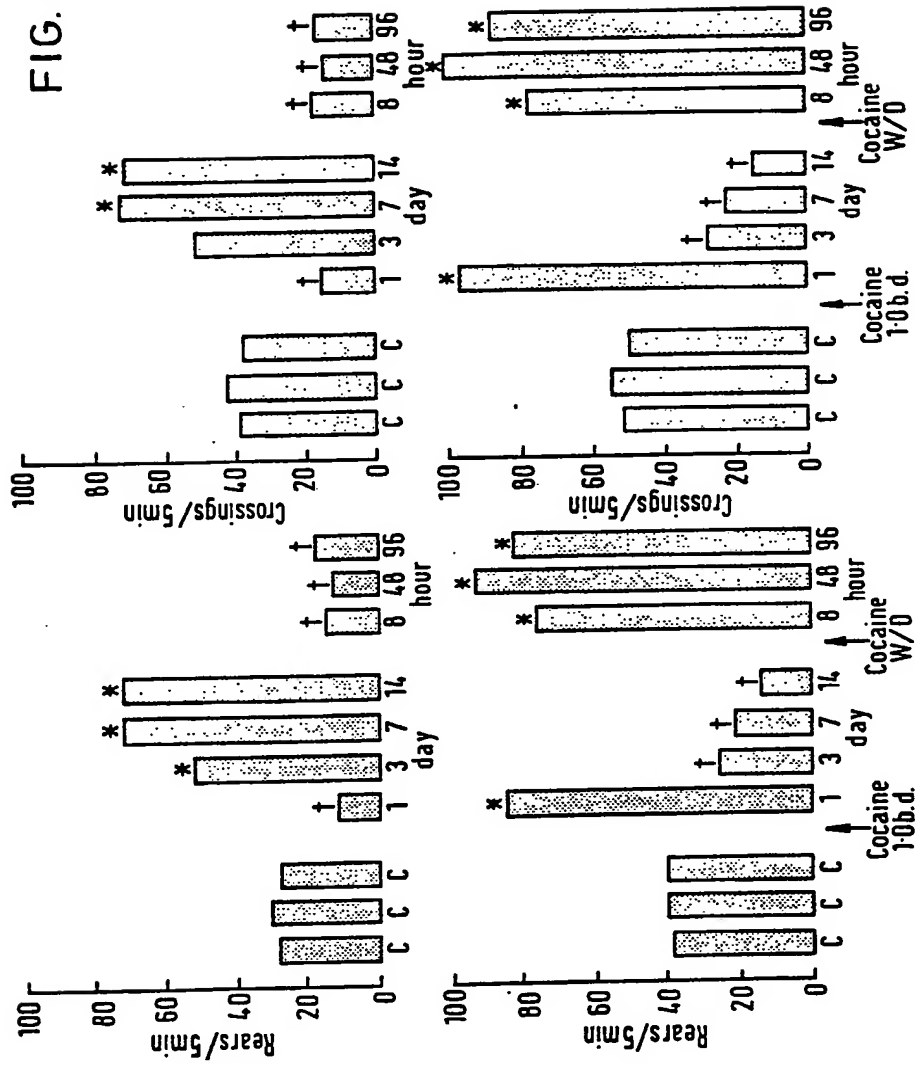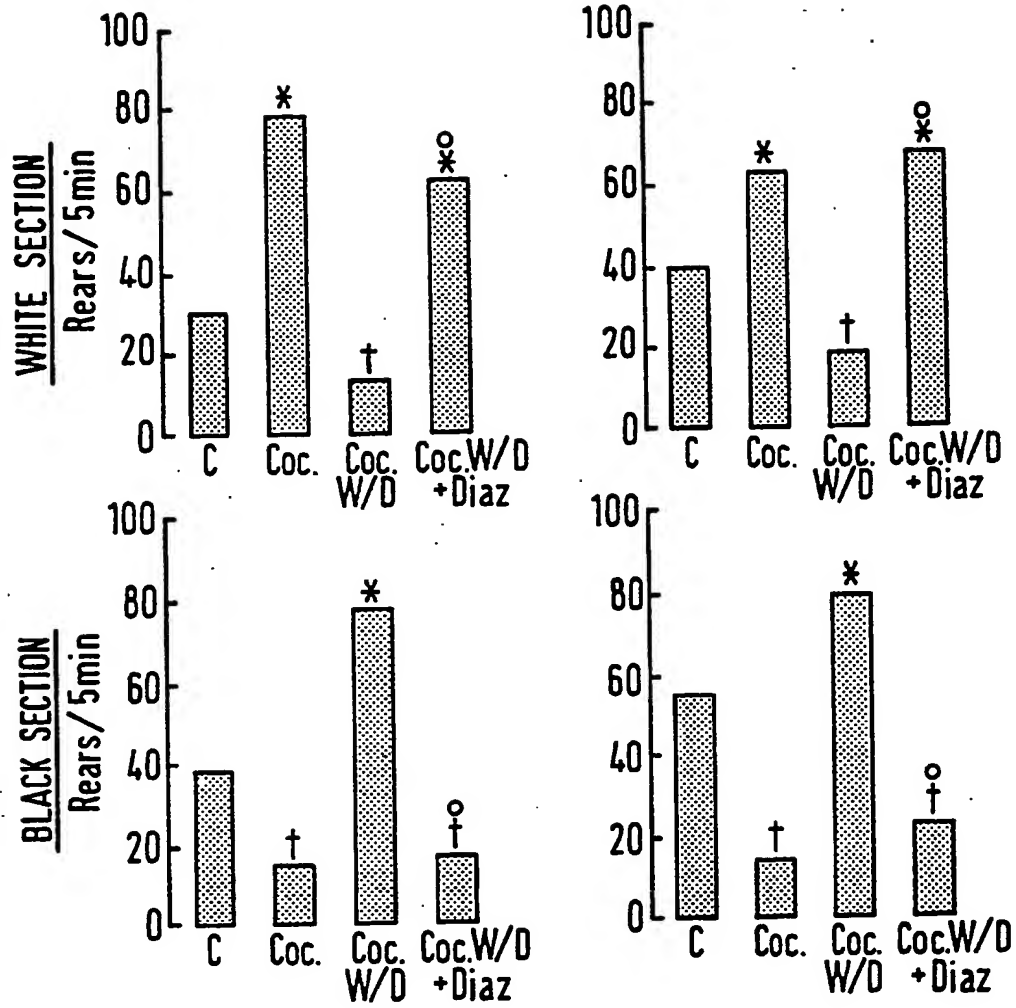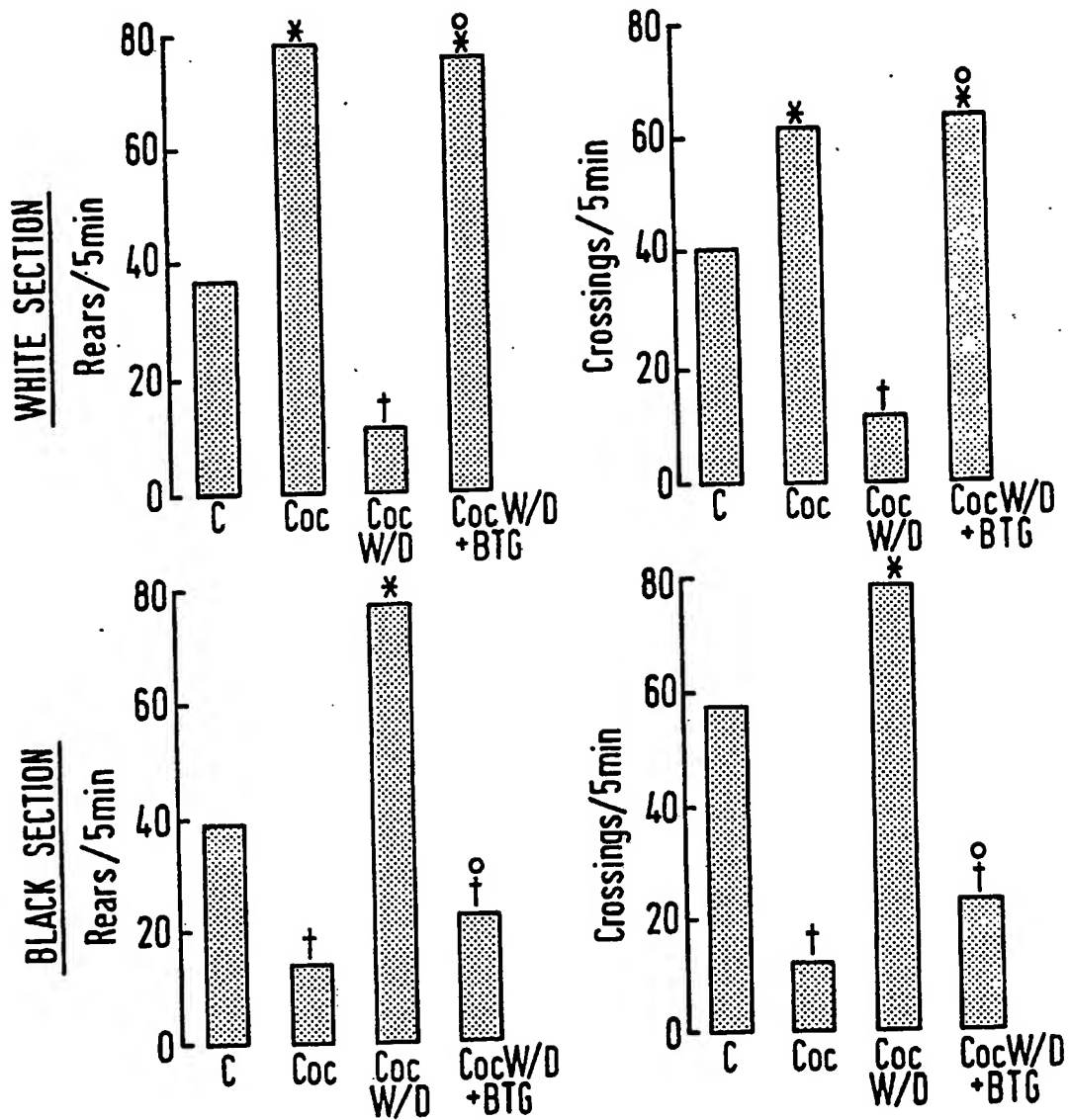FIG. 6.
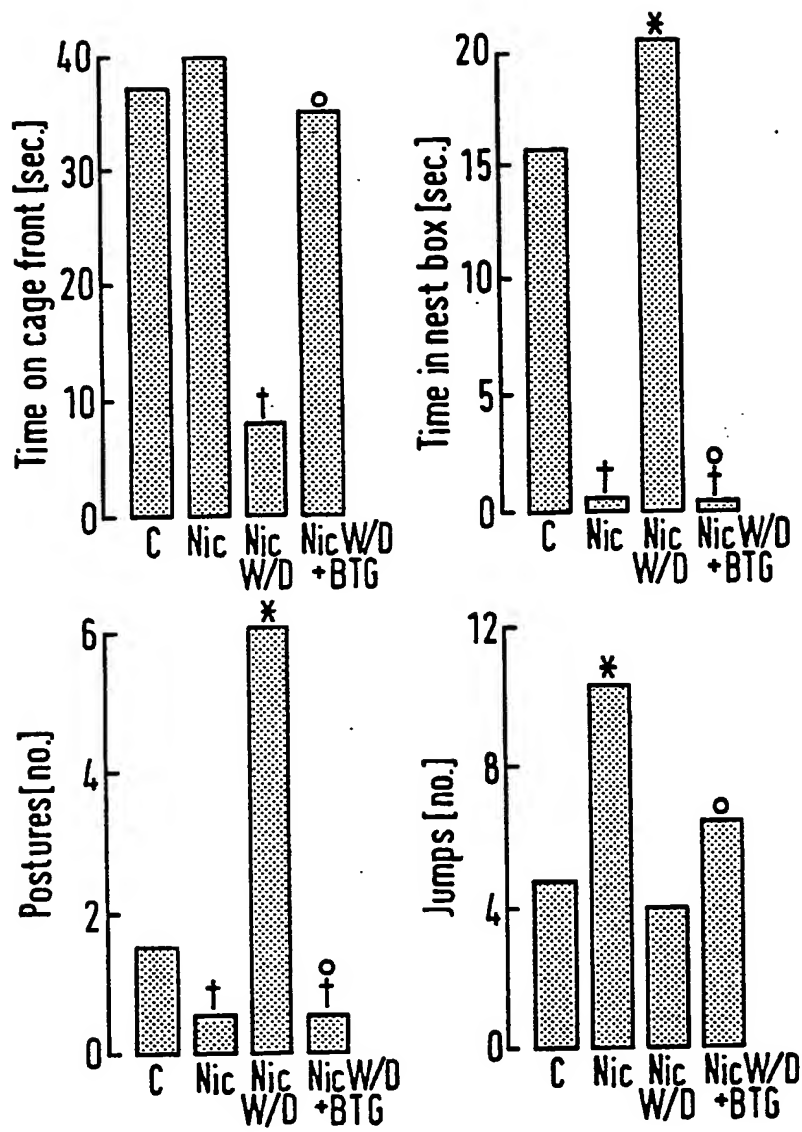
FIG. 7.

FIG. 8.

FIG. 9.

FIG. 10.

ANTI-ANXIOGENIC COMPOSITIONS CONTAINING

DIOXOPIPERIDINE DERIVATIVES

This invention relates to the use of certain
3-phenyl-3-aminoalkyl-4-methyl-2,6-dioxopiperidines to

05   antagonise anxiogenesis associated with withdrawal from
drug addiction. In particular, the invention provides
the use of the said dioxopiperidines in the manufacture
of medicaments for the treatment of said anxiogenesis
and methods of treatment of said anxiogenesis using.

10   said dioxopiperidines.

It has been recognised in recent years that
anxiogenesis is a substantial problem associated with
the withdrawal from drug addiction. Many addictive
drugs, such as alcohol, nicotine and cocaine, are

15   anxiolytic and when the drug is abruptly withdrawn
anxiogenesis usually develops. The severity and
duration of the anxiogenesis generally depends upon the
duration of the addiction. Anxiogenesis also is
encountered with withdrawal from narcotic and other

20   drugs producing physical dependance.

Benzodiazepines agonists especially diazepam, have
been used to treat anxiogenesis associated with drug,
especially alcohol, withdrawal. However, sedative,
rather than anti-anxiety, doses have been employed and

25   treatment often results in substitution of the original
drug addiction for benzodiazepine addiction. Anxiolytic
drugs generally have not been considered of use in the

treatment of anxiogenesis associated with addictive

drug withdrawal because of the substantial dose levels

required and the risk of substitute addiction.

It has surprisingly now been found that certain

05   3-phenyl-3-aminoalkyl-4-methyl-2,6-dioxopiperidines (as

defined hereinafter) potently antagonise anxiogenesis

associated with addictive drug withdrawal.

GB 1455687 (also AU 480855, BE 808958, DE

23630526, FR 7346904, JP 6053014 and US 3963729)

10   discloses that 3-phenyl-3-aminoalkyl-4- and/or

5-methyl-2,6-dioxopiperidine derivatives have central

nervous system, especially antidepressant, activity.

Said compounds include, <u>inter alia</u>, those of the

following Formula A.

15
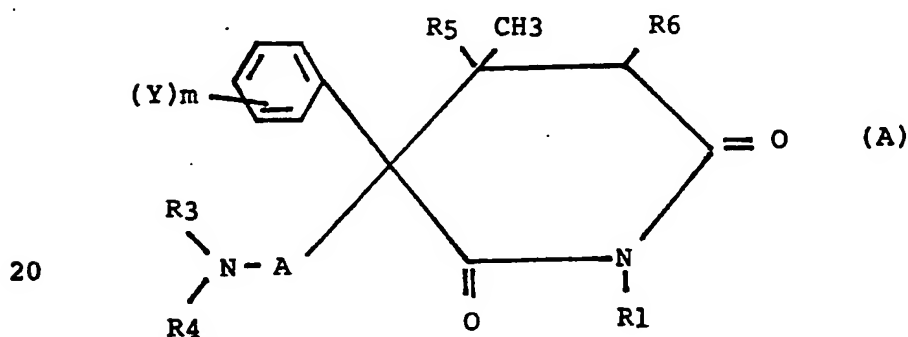
wherein:

R1 represents hydrogen or C1-C4 alkyl;

R3 represents hydrogen or C1-C4 alkyl;

25   R4 represents C1-C4 alkyl;

R5 and R6 independently represent hydrogen or

methyl;

A represents C_1-C_6 alkylene;

m is 0 to 3; and

Y is hydroxy, C_1-C_4 alkoxy, C_1-C_4 alkyl,

05 C_1-C_4 hydroxyalkyl, halogen or trifluoromethyl.

The dose level specified for administration of the compounds is 0.1 to 100 mg/kg using pharmaceutical compositions containing 1 to 1000 mg per unit dose.

It also has been disclosed in U.S. 4,461,771 that

10 compounds of Formula A, in which R_1 represents hydrogen; R_3 and R_4 independently represent methyl or ethyl; R_5 represents methyl; R_6 represents hydrogen; A represents ethylene or propylene; m is 1 or 2; and each Y is in a meta position and independently

15 represents hydroxy or C_1-C_2 alkoxy, are believed to reduce in vitro the activity of tryptophan hydroxylase by blocking the depolarization-induced activation of the enzyme in the brain stem and hence are of potential use in the prophylactic treatment of the stressful

20 disorder migraine. The dose level specified for this treatment is 0.01 to 10 mg/kg, especially 0.1 to 3 mg/kg, using pharmaceutical compositions containing 0.1 to 200 mg, usually 1 to 100 mg, per unit dose. More recently, it has been reported that at least one

25 compound of Formula A (viz 3-(3'-methoxy-phenyl)-3-

(3"-N,N-dimethylaminopropyl)-4,4-dimethyl-2,6-dioxo-

piperidine; AGN 2979) also blocks in vitro the

activation of tryptophan hydroxylase resulting from

exposure of brain stem slices to metabolic inhibitors

05 or methylxanthines or induced by incubation of

supernatant preparations of the enzyme under

phosphorylating conditions (Boadle-Biber, M.C. et al

Biochem. Pharmacol. 35, 1521-6, (1986)). However, it

also has been reported that AGN 2979 has no significant

10 effect in vitro upon the unactivated enzyme

(Boadle-Biber, M.C. et al supra).

Further, it has recently been disclosed in GB

2181346A that compounds of Formula A, in which R_1

represents hydrogen; R_3 and R_4 independently

15 represent methyl or ethyl; A represents ethylene or

propylene; m is 1 or 2; and each Y is in a meta

position and independently represents hydroxy or

C_1-C_2 alkoxy, are believed to reduce the turnover

of 5-hydroxytryptamine (5HT) resulting from inhibiting

20 the activity of tryptophan hydroxylase. They are

reported to have anxiolytic activity, antagonize the

anxiogenic activity of benzodiazepines inverse

agonists, reduce chronic abnormally high brain levels

of 5HT or its metabolite 5-hydroxy-indoleacetic acid,

25 and have antibacterial and antiviral activity.

G.B. 2181346A was published in pursuance of U.K. Patent Application No. 8621577 filed 8th September 1986 and claiming priority from U.K. Patent Applications Nos. 8522455 (filed 11th September 1985), 8603909

05 (filed 17th February 1986) and 8603910 (also filed 17th February 1986). Originally, it was thought that the disclosed compounds were not themselves anxiolytic because they have virtually no action at benzodiazepine receptors and that they acted via some unknown

10 pharmacological mechanism to potentiate the anxiolytic activity of benzodiazepine receptors. Their anxiolytic activity was disclosed for the first time in U.K. Patent Application No. 8621577. At that time, the compounds were believed to be active in the range 0.1

15 to 20 mg/kg, especially 0.5 to 10 mg/kg and hence pharmaceutical compositions containing 10 to 500 mg, especially 10 to 100 mg, were proposed. It was subsequently surprisingly found that the compounds are active at much lower dose levels, down to nanogram/kg

20 amounts.

According to a first aspect of the present invention, there is provided the use in the manufacture of a medicament for the treatment of anxiogenesis associated with addictive drug withdrawal of a compound

25 of the following Formula I.
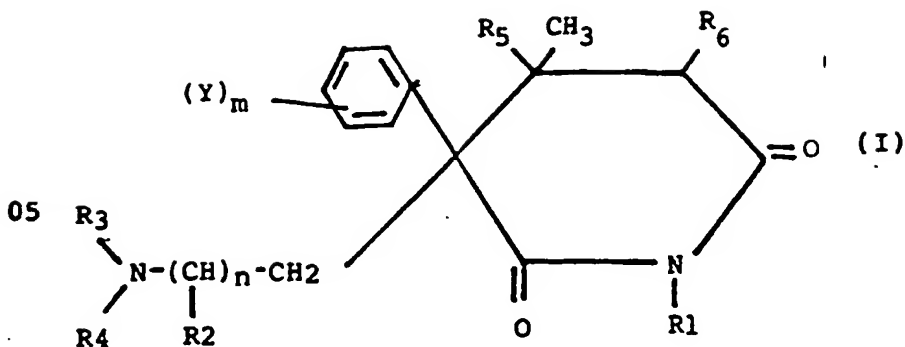
wherein:

R1 represents hydrogen or C1-C4 alkyl;

n is 1 or 2;

R2 represents hydrogen or methyl, provided that one R2 is hydrogen when n is 2;

n is 1 or 2;

R2 represents hydrogen or methyl, provided that one R2 is hydrogen when n is 2;

R3 represents hydrogen or C1-C2 alkyl;

R4 represents C1-C2 alkyl;

R5 and R6 independently represent hydrogen or methyl;

m is 0 to 3; and

each Y is in a meta or para position and independently represents hydroxy, C_1-C_2 alkoxy, C1-C2 alkyl, C1-C2 hydroxyalkyl, halogen, or trifluoromethyl, provided that hydroxy and alkoxy are not in the para position,

or a pharmacologically acceptable salt thereof.

In a second aspect, the invention provides a method of treating a patient suffering from anxiogenesis associated with addictive drug withdrawal, which comprises administering to the

05 patient an anti-anxiogenic effective amount of a compound of the following Formula I.

10

$$\text{(Y)}_m \quad \text{R}_5 \quad \text{CH}_3 \quad \text{R}_6 \quad =O \quad (I)$$

$$\underset{\text{R4}}{\overset{\text{R3}}{>}}N-(CH)_n-CH_2 \quad \overset{\|}{O} \quad \underset{\text{R1}}{\overset{N}{|}}$$
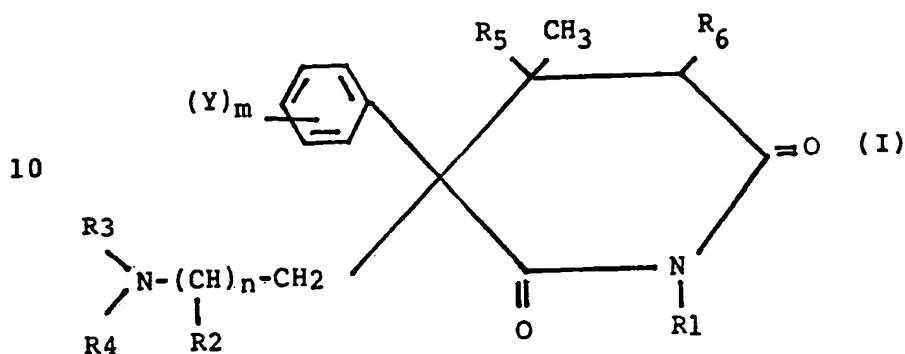
wherein:

15   R_1 represents hydrogen or C_1-C_4 alkyl;

$\underline{n}$ is 1 or 2;

R_2 represents hydrogen or methyl, provided that one R_2 is hydrogen when $\underline{n}$ is 2;

R_3 represents hydrogen or C_1-C_2 alkyl;

20   R_4 represents C_1-C_2 alkyl;

R_5 and R_6 independently represent hydrogen or methyl;

$\underline{m}$ is 0 to 3; and

each Y is in a meta or para position and

25 independently represents hydroxy, C_1-C_2 alkoxy, C_1-C_2 alkyl, C_1-C_2 hydroxyalkyl, halogen, or

trifluoromethyl, provided that hydroxy and alkoxy are

not in the para position,

or a pharmacologically acceptable salt thereof.

The compounds of Formula I can be prepared in the

05 manner disclosed in GB 1455687. They exist as optical

isomers and can be used in racemate form or as

individual (+) or (-) isomers. Presently, the (-)

isomer is preferred.

As mentioned above the compounds of Formula 1

10 antagonise anxiogenesis associated with addictive drug

withdrawal and hence are useful in the treatment of

said withdrawal. Unlike benzodiazepine agonists, they

do not cause sedation at high doses (10^2 mg/kg). In

the treatment of withdrawal from alcohol, nicotine,

15 cocaine and other addictive drugs not causing physical

dependence, they can be used alone. However, in the

treatment of narcotic and the like physically addictive

drugs, they will be used with drugs required to treat

the physical aspects of the drug withdrawal.

20 The compounds of Formula I can be administered in

various manners to achieve the desired anxiogenic

effect. The compounds can be administered enterally or

parenterally to the patient being treated. Oral

administration is likely to be the preferred route in

25

most circumstances but injection, especially

subcutaneously or intravenously, will be preferred in

some circumstances.

05

The amount of compound administered will vary and

can be any anti-anxiogenic effective amount. Depending

upon the patient and the mode of administration, the

amount of compound administered may vary over a wide

10   range to provide from about 10^{-7} to 10^2 mg/kg,

usually 10^{-5} to 10^2 mg/kg, especially 10^{-4} to

10^2 mg/kg, of body weight of the patient per unit

dose. Unit doses of these compounds can contain, for

example, from about 10^{-6} mg to 500 mg, usually

15   10^{-4} to 10^2 mg, especially 10^{-3} to 10^2 mg

of the compound and may be administered, for example,

from 1 to 4 times daily.

The compounds of Formula I have virtually no

20   action at benzodiazepine receptors. The capacity of a

selected number of compounds of Formula I to displace

triturated flunitrazepam from benzodiazepine receptors

has been measured with the results set forth in Table I

below:-

25

TABLE 1

	COMPOUND OF FORMULA I				
	2979	3222	2939	3181	DIAZEPAM*
IC_{50}(uM) [^{3}H]Flunitr-azepam Binding	350	1300	9000	6700	0.014

*   7-chloro-1,3-dihydro-1-methyl-5-phenyl-

-2H-1,4-benzodiazepine-2-one

The term "unit dosage form" is used herein to mean
a single or multiple dose form containing a quantity of
the active ingredient in admixture with or otherwise in
association with a diluent or carrier, said quantity
being such that one or more predetermined units are
normally required for a single therapeutic
administration. In the case of multiple dose forms
such as liquids or scored tablets, said predetermined
unit will be one fraction, such as a 5 ml (teaspoon)
quantity of a liquid or a half or quarter of a scored
tablet; of the multiple dose form.

The compounds of general Formula I can have the

phenyl moiety substituted in one or both meta positions
by C_1-C_2 alkyl, C_1-C_2 hydroxyalkyl, halogen,
trifluoromethyl, or, preferably, hydroxy or C_1-C_2
alkoxy. Additionally or alternatively, the phenyl
05 moiety can be substituted in the para position by the
aforementioned groups other than hydroxy and alkoxy.
It is presently preferred that the substituent(s)
should be hydroxy or, especially, methoxy. It is also
preferred that one or both meta positions are
10 substituted and that, when there are two substituents,
they should be the same.

The amino group of the compounds of Formula I can
be secondary or tertiary having methyl or ethyl groups
attached to the nitrogen atom. Dimethylamino presently
15 is preferred. The amino group is connected to the
piperidine ring by a divalent ethylene (i.e. n = 1) or
trimethylene (i.e. n = 2) radical optionally
substituted on a carbon atom not adjacent said ring
with a methyl group. Presently, unsubstituted
20 trimethylene is preferred.

The piperidine ring of the compounds of Formula I
is substituted in the 4-position with methyl and
optionally by one or two further methyl groups in the 4
and/or 5 positions. It is presently preferred that
25 there is one further methyl group in the 4 or 5
position, especially in the 4-position.

The ring nitrogen atom of the piperidine ring can be substituted with a C_1-C_4 alkyl group but it is presently preferred that said nitrogen atom is unsubstituted.

05   The C_1-C_2 alkyl groups or moieties referred to herein are methyl or ethyl; methyl presently being preferred. The C_3-C_4 alkyl groups which may be substituents on the nitrogen atom of the piperidine ring can be straight or branched chain but the straight

10   chain n-propyl or n-butyl groups presently are preferred. The halogen substituent(s) in the phenyl ring can be chlorine, bromine, or fluorine; chlorine presently being preferred.

The presently preferred compounds of Formula I are

15   those of the following Formula IA.
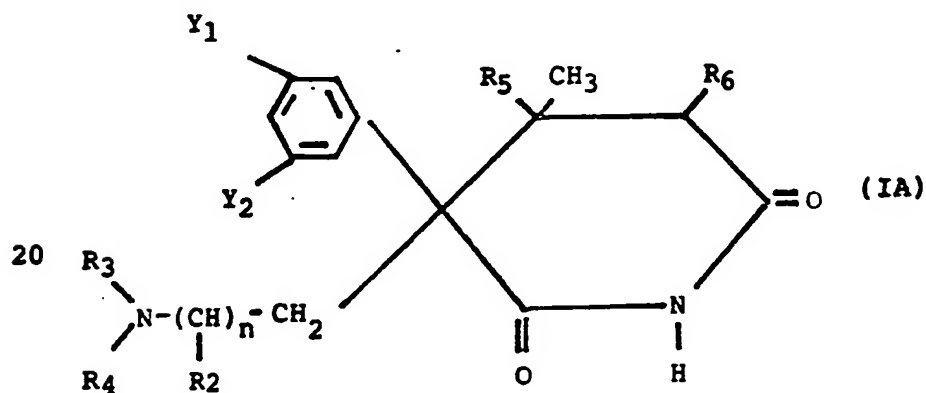
wherein:

n is 1 or 2;

25   R_2 represents hydrogen or methyl, provided that one R_2 is hydrogen when n is 2;

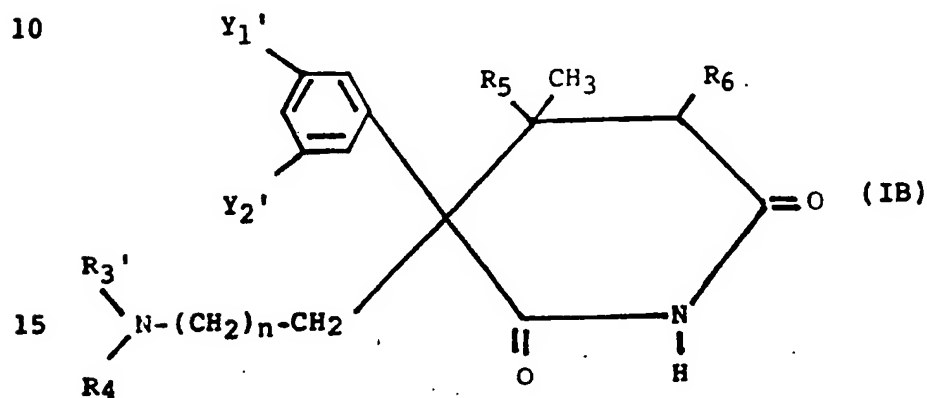R_3 represents hydrogen or C_1-C_2 alkyl;

R_4 represents C_1-C_2 alkyl;

R_5 and R_6 independently represent hydrogen or methyl; and

05   Y_1 and Y_2 independently represent hydrogen, hydroxy or C_1-C_2 alkoxy,

or a pharmacologically acceptable salt thereof.

The presently especially preferred compounds of Formula 1A are those of the following Formula IB.

10

(IB)

wherein:

$\underline{n}$ is 1 or 2;

R_3' and R_4 independently represent C_1-C_2

20 alkyl;

R_5 and R_6 independently represent hydrogen or methyl;

Y_1' represents hydroxy or C_1-C_2 alkoxy; and

Y_2' represents hydrogen, hydroxy or C_1-C_2

25 alkoxy,

or a pharmacologically acceptable salt thereof.

Examples of compounds of Formula IC include the following:-

3-(3'-methoxyphenyl)-3-(2"-N,N-dimethylaminoethyl)-4,4-dimethyl-2,6-dioxopiperidine

05 3-(3'-methoxyphenyl)-3-(3"-N,N-dimethylaminopropyl)-4,4-dimethyl-2,6-dioxopiperidine (AGN 2979);

3-(3'-methoxyphenyl)-3-(2"-N,N-diethylaminoethyl)-4,4-dimethyl-2,6-dioxopiperidine;

3-(3'-methoxyphenyl)-3-(3"-N,N-diethylaminopropyl)-

10 4,4-dimethyl-2,6-dioxopiperidine;

3-(3'-hydroxyphenyl)-3-(2"-N,N-dimethylaminoethyl)-4,4-dimethyl-2,6-dioxopiperidine;

3-(3'-hydroxyphenyl)-3-(3"-N,N-dimethylaminopropyl)-4,4-dimethyl-2,6-dioxopiperidine;

15 3-(3'-methoxyphenyl)-3-(2"-N,N-dimethylaminoethyl)-4,5-dimethyl-2,6-dioxopiperidine (AGN 2939);

3-(3'-methoxyphenyl)-3-(3"-N,N-dimethylaminopropyl)-·
4,5-dimethyl-2,6-dioxopiperidine (AGN 3181);

3-(3'-ethoxyphenyl)-3-(3"-N,N-dimethylaminopropyl)-

20 4,4-dimethyl-2,6-dioxopiperidine;

3-(3'-ethoxyphenyl)-3-(3"-N,N-diethylaminopropyl)-4,4-dimethyl-2,6-dioxopiperidine;

3-(3',5'-dimethoxyphenyl)-3-(3"-N,N-dimethylamino-propyl)-4,4-dimethyl-2,6-dioxopiperidine (AGN 3222);

25 3-(3',5'-dimethoxyphenyl)-3-(2"-N,N-dimethylamino-ethyl)-4,4-dimethyl-2,6-dioxopiperidine;

3-(3',5'-dimethoxy phenyl)-3-(3"-N,N-dimethylamino-

propyl)-4,5-dimethyl-2,6-dioxopiperidine; and

3-(3',5'-dimethoxyphenyl)-3-(2"-N,N-dimethylamio-

ethyl)-4,5-dimethyl-2,6-dioxopiperidine;

05   Examples of other compounds of Formula I

include:-

3-phenyl-3-(2'-N,N-dimethylaminoethyl)-4-methyl-2,6-

dioxopiperidine;

3-phenyl-3-(2'-N,N-dimethylaminoethyl)-4,4-dimethyl-2,6

10   -dioxopiperidine;

3-phenyl-3-(2'-N,N-dimethylaminoethyl)-4,5-dimethyl-2,6

-dioxopiperidine;

3-phenyl-3(3'-N,N-dimethylaminopropyl)-4,4-dimethyl-2,6

-dioxopiperidine;

15   3-(4'-chlorophenyl)-3(3"-N,N-dimethylaminopropyl)-4,4-

dimethyl-2,6-dioxopiperidine; and

3-phenyl-3(2' N-methylaminoethyl)-4,4-dimethyl-2,6-

dioxopiperidine.

The compounds of Formula I may be administered in

20   free base form, as an alkali metal or alkaline earth

metal salt or as a pharmaceutically acceptable acid

addition salt with the proviso that an alkali metal or

alkaline earth metal salt is not normally combined with

an acid addition salt except in a layer formulation.

25

Representative acid addition salt forms include organic acid salt forms such as the maleate and methane sulphonate and mineral acid salt forms such as the hydrochloride and perchlorate.

05   The pharmaceutical formulations in which form the active compounds of the invention will normally be utilized are prepared in a manner well known *per se* in the pharmaceutical art and usually comprise at least one active compound of Formula I in admixture or

10   otherwise in association with a pharmaceutically acceptable carrier or diluent therefor. For making those formulations the active ingredient will usually be mixed with a carrier, or diluted by a diluent, or enclosed or encapsulated in a capsule, sachet, cachet,

15   paper or other container. A carrier or diluent may be solid, semi-solid or liquid material which serves as a vehicle, excipient or medium for the active ingredient. Suitable carriers or diluents are well known *per se*.

The formulations may be adapted for enteral or

20   parenteral use and may be administered to the patient in the form of tablets, capsules, dragees, suppositories, syrups, suspensions, subcutaneous or intramuscular depot injections or implants or the like. The formulations may be in delayed or sustained release

25   form.

Aside from the active agents the compositions may contain pharmaceutically inert organic or inorganic

adjuvants, optionally granulating agents, binding agents lubricants, dispersing agents, wetting agents and preservatives. Moreover, the pharmaceutical compositions may contain colouring, flavouring and

05 sweetening substances. Adjuvants for the production of tablets may be e.g. calcium carbonate, lactose micro-crystalline cellulose, mannitol or talc. Starch and alginic acid or micro-crystalline cellulose may be used as granulating and disintegrating agents, starch,

10 polyvinylpyrrolidone and gelatine may be used as binding agents and magnesium stearate, stearic acid, colloidal silica and talc as lubricants. Tablet formulation may be coated or uncoated, the coating having the purpose of delaying the disintegration and

15 absorption in the gastrointestinal tract. Suitable suspending agents for the production of liquid administration forms are e.g. methyl cellulose and sodium alginate. Capsule formulation may contain the active agents on their own or together with an inert

20 solid diluent e.g. calcium phosphate, corn starch, lactose, or mannitol.

The invention is illustrated in the following non-limiting Examples.

25

EXAMPLE 1

Tablet Formulation

Tablets each having the following composition are prepared by conventional techniques:

05
		mg/tablet
(a)	Compound AGN 2979 base	1
(b)	Lactose	51.5
(c)	Maize starch dried	45
(d)	Magnesium stearate	1.5

10
EXAMPLE 2

Suppository Formulation

		mg/suppository
(a)	Compound AGN 2979 HCl	10
(b)	Oil of Theobroma (cocoa butter)	990

15 The compound (a) is powdered and passed through a BS No. 100 sieve and triturated with molten oil of Theobroma at 45°C to form a smooth suspension. The mixture is well stirred and poured into moulds each of nominal 1 G capacity to produce suppositories.

20
EXAMPLE 3

Tablet Formulation

(a)	Compound AGN 2979 base	10mg
(b)	Wheat starch	7g
(c)	Lactose	20g
25 (d)	Magnesium Stearate	1g

EXAMPLE 4

Pill Formulation

<u>per pill</u>

05   (a) Compound AGN 2979 HCl   10mg

           (b) Corn starch   45mg

           (c) Liquid glucose   7ml

The pills are prepared by blending the active ingredient (a) and the corn starch, then adding the

10   liquid glucose with thorough kneading to form a plastic mass from which the pills are cut and formed.

EXAMPLE 5

Gelatine Capsule Formulation

<u>per capsule</u>

15   (a) Compound AGN 2979 HCl   2.5mg

           (b) Talc   70mg

A capsule is prepared by passing dry powdered active ingredient (a) and powdered talc in the above proportions through a fine mesh screen and mixing them

20   well. The powder is then filled into hard gelatin capsules at a net fill of 72.5mg per capsule.

25

EXAMPLE 6

Naïve male albino BKW mice, 25-30g, were used in all experiments. 10 mice were normally housed in each cage and kept on a 12 h light/dark cycle with lights off at 08.00h.

05   The apparatus used for the detection of changes in exploratory behaviour consisted of an open-topped box (45 x 27 x 27 cm high) lined into a 9 cm squares, one third painted black and illuminated under a dim red light (1 x 60W) and partitioned from the remainder of

10 the box which was painted white and brightly illuminated with a 100W light source located 17 cm above the box. An opening 7.5 x 7.5 cm located at floor level in the centre of the partition allowed access between the black and white areas.

15   Tests were conducted between 13.00 and 18.00h in a quiet darkened room illuminated with a red light. Animals which had been subject to alcohol (8% w/v in drinking water) were taken for testing either during alcohol intake or following its withdrawal with or

20 without concomitant drug (diazepam or AGN 2979) treatment. Mice were taken from a dark holding room in a dark container to the dark testing room where, after a period of adaptation to the environment of the test room, they were placed individually into the centre of

25 the white, brightly-lit area of the test box and their

behaviour observed over a 5 min period by remote video recording. The behaviours noted were (a) the number of exploratory rearings in the white and black sections, (b) the number of line crossings in the white and black areas (c) the number of transitions between the white

05 and black or black and white areas, (d) the time spent in the white and black areas and (e) latency of movement from the white to black area.

The anxiogenesis of alcohol withdrawal is maximum

10 at 24 and 48h following removal of alcohol intake. Diazepam (10 mg/kg i.p.) or AGN 2979 (0.5 mg/kg i.p.) were given at the time of alcohol withdrawal and then b.d. until testing 48h after alcohol withdrawal.

During the intake of alcohol, mice exhibit marked

15 anxiolysis characterised by increased exploratory behaviour in the white section of the test box, with corresponding decreases in the black (Figure 1). The anxiolysis is also seen in the delayed latency for movement from the white to the black, and a reduction

20 in the % of time spent in the black. When the alcohol is withdrawn, a reverse behavioural profile of anxiogenesis is observed. This becomes apparent within 24h of withdrawal and persists for longer than 48h. The intensity of this anxiogenesis of withdrawal from

25 alcohol is exemplified by the data given on Figure 1 showing markedly reduced activity in the white section

of the test box, with correspondingly marked elevations in exploratory activity in the black.

The anxiogenesis of alcohol withdrawal can be antagonised by diazepam (10 mg/kg given b.d., Figure 2)

05 or by AGN 2979 (0.5 mg/kg given b.d., Figure 3). It is interesting that relatively large doses of anxiolytic agents are required to antagonise the alcohol withdrawal anxiogenesis, and that treatment should ideally commence at the time of withdrawal with

10 subsequent b.d. dosing (during this time tolerance rapidly develops to the sedative actions of diazepam).

It can be seen from Figures 2 and 3 that, when effective, both diazepam and AGN 2979 not only reverse the anxiogenesis but actually lead to anxiolysis.

15 Diazepam and AGN 2979 appear to be equieffective to combat the anxiogenesis of alcohol withdrawal, but AGN 2979 is considerably more potent and is devoid of the initial sedative actions seen on treatment with diazepam.

20   EXAMPLE 7

The procedure of Example 6 was repeated with mice given nicotine (0.1 mg/kg b.d.) for 14 days. They were tested during nicotine intake and then 8; 48 and 96 h after nicotine withdrawal. The number of exploratory

25 rearings and the number of line crossings in the black and white areas were noted. Anxiogenesis of withdrawal

was marked at 48 h and the actions of diazepam and AGN
2979 were determined at this time. The diazepam and
AGN 2979 were given at the time of nicotine withdrawal
and then b.d. until testing. The mice were used once

05 only and each testing time utilised naive animals in
groups of 5-10.

Figure 4 shows the anxiolytic action of nicotine
(0.1 mg/kg i.p. b.d. 14 days) and anxiogenesis
following withdrawal of the nicotine treatment in mice

10 tested in the black:white box. C indicates the
response of vehicle-treated mice (responses
indistinguishable from those of normal, untreated
mice). n = 6. S.E.M.s less than 11.13%, *,+P less
than 0.001 (Student's t test).

15 Figure 5 shows the antagonism of nicotine (Nic.)
withdrawal (W/D) anxiogenesis (0.1 mg/kg b.d. 7 days,
48 h W/D) by diazepam (1.0 mg/kg i.p.) in the mouse.
C = control, Nic. = during nicotine treatment, Nic. W/D
= during nicotine withdrawal, Nic. W/D + Diaz =

20 diazepam given during nicotine withdrawal. n = 6.
S.E.M.s less than 12.7%, *,+P less than 0.01 - P less
than 0.001 (compared to C), °P less than 0.001
(reversal of withdrawal)(Student's t test).

Figure 6 shows the antagonism of nicotine

25 withdrawal (W/D) anxiogenesis (0.1 mg/kg b.d. 7 days,
48 h W/D) by AGN 2979 (1.0 mg/kg s.c.) in the mouse.

C = control, Nic. = during nicotine treatment, Nic. W/D
= during nicotine withdrawal Nic. W/D + BTG = AGN 2979
given during nicotine withdrawal. n = 6. S.E.M.s less
than 11.2%, *,+P less than 0.001 (compared to C), *P

05 less than 0.001 (reversal withdrawal)(Student's t
test).

Anxiolysis presented throughout a 14 day period of
treatment of mice with nicotine, 0.1 mg/kg b.d. This
was revealed in the black:white test box as a reduced

10 aversion to the white, brightly-lit environment
(increased exploratory rearings and line crossings in
the white, correspondingly decreased in the black, Fig.
4). This anxiolysis was reversed to anxiogenesis 8 -
96 h after withdrawing the nicotine treatment. This

15 was seen in the black:white test box as increased
exploratory rearings and line crossings in the black,
dimly-lit area, with corresponding reductions in
behaviour in the white compartment (Fig. 4).

The anxiogenesis of nicotine withdrawal could be

20 antagonised by treatments with diazepam or AGN 2979
(Figs. 5 and 6). Both compounds were effective at 1
mg/kg at which doses the anxiogenesis was reversed to
anxiolysis. However, at this dose level diazepam
causes sedation but AGN 2979 does not.

25   EXAMPLE 8

The procedure of Example 7 was repeated with mice

given cocaine (1.0 mg/kg b.d.) for 14 days. As in said

Example, the mice were treated at cocaine intake and at

8, 48 and 96 h after cocaine withdrawal. On this

occasion, anxiogenesis of cocaine withdrawal was marked

05 at 8 h and the actions of diazepam and AGN 2979, given

at the time of cocaine withdrawal, were determined at

this time.

Figure 7 shows the anxiolytic action of cocaine

(1.0 mg/kg b.d. 14 days) and anxiogenesis following its

10 abrupt withdrawal, measured using the mouse black:white

test box. n = 6. S.E.M.s less than 11.9%. *,+P less

than 0.05 - P less than 0.001 (Student's t test,

comparsion to C, control).

Figure 8 shows the antagonism of cocaine withdrawal

15 (W/D) anxiogenesis in the mouse (1.0 mg/kg b.d. 14

days, W/D 8 h) by diazepam (10 mg/kg) as measured in

the black:white test box. C = control, Coc. = during

cocaine, Coc. W/D = during cocaine withdrawal, Coc. W/D

+ Diaz. = during cocaine withdrawal but with diazepam

20 administered at the time of withdrawal. n = 6. S.E.M.s

less than 12.7%. *,+P less than 0.001 (compared to

C). °P less than 0.001 (reversal W/D)(Student's t

test).

Figure 9 shows the antagonism of cocaine withdrawal

25 (W/D) anxiogenesis in the mouse (1.0 mg/kg b.d. 14

days, W/D 8 h) by AGN 2979 (1 mg/kg s.c.) as measured

in the mouse black:white test box. C = control, Coc. =
during cocaine, Coc. W/D = during cocaine withdrawal,
Coc. W/D + BTG = during cocaine withdrawal but with AGN
2979 administered at the time of withdrawal. n = 6.

05 S.E.M.s less than 12.1%, *,+P less than 0.001
(compared to C). °P less than 0.001 (reversal W/D)
(Student's t test).

In the mouse, long-term treatment with cocaine
caused anxiolysis, after an initial stage of

10 anxiogenesis on day 1. The anxiolysis was apparent on
days 3 - 14 of treatment (Fig. 7). Anxiogenesis
followed the withdrawal of treatment with cocaine, and
was detected 8 - 96 h following withdrawal (Fig. 7).

The anxiogenesis of cocaine withdrawal was

15 antagonised by diazepam at 10 mg/kg (Fig. 8) and by
AGN 2979 at 1 mg/kg (Fig. 9). However, at these dose
levels diazepam causes sedation but AGN 2979 does not.

EXAMPLE 9

Male laboratory bred common marmosets (Callithrix

20 jacchus), weighing between 350-400g, were housed in
single sex pairs and allowed food (mazuri primate diet
S.D.S. Ltd., Essex) ad libitum. Once daily marmosets
were also given an assortment of fruit and brown or
malt bread. Holding rooms were maintained at 25 ± 1 °C

25 at a humidity of 55% and on a 12 h light/dark (red
illumination) cycle (with simulated dawn and twilight

periods) with lights on at 07.00 h.

Tests were conducted between 13.00 - 15.30 h in the normal holding room (to avoid unwanted disruption of behaviour by movement to a novel room or cage). The

05 holding cages, in which the marmosets were housed individually, measured 76 cm high, 50 cm wide and 60 cm deep. "Anxiety" was initiated by a human observer standing 0.6 m in front of the holding cage. Changed behaviour was recorded over a 10 minute period

10 (consecutive 2 minute recordings for each behavioural response(s) were measured) both by the observer and by blind assessment by an independent observer of video recordings taken throughout the period of human threat. The behavioural measures noted included (a) time spent

15 on cage front in direct confrontation with the human threat, (b) the number of aggressive body postures, primarily shown as raising of the tail to expose the genital region with varying degrees of body piloerection, anal scent marking and slit stare with

20 flattened ear tufts, (c) time spent in nest box avoiding confrontation with the human observer (threat) and (d) number of jumps to and from the cage front which indicates investigation of the situation and reduced apprehension.

25 The marmosets were given nicotine (0.01 mg/kg s.c. b.d.) for 7 days. They were tested on day 5 of

nicotine intake and then 48 h after nicotine
withdrawal. Anxiogenesis of withdrawal was marked at
48 h and the actions of AGN 2979 were determined at
this time (a single dose given 40 min before testing).

05   Figure 10 shows the antagonism of nicotine (Nic.)
withdrawal (W/D) anxiogenesis (0.01 mg/kg s.c. b.d. 7
days, 48h) by AGN 2979 (0.01 mg/kg s.c., 40 min
treatment) in the marmoset. Nic = during nicotine
treatment (day 5), Nic. W/D = during nicotine

10 withdrawal, Nic. W/D + BTG = AGN 2979 given during
nicotine withdrawal. n = 3. S.E.M.s 11 - 23%. *,+P
less than 0.05 - P less than 0.001 (compared to C), °P
less than 0.001 (reversal withdrawal) (Student's t
test).

15   During nicotine treatment marmosets, similarily to
mice, exhibited reduced anxiety responding. In the
marmoset human threat test this was seen as reduced
time spent in the nest box avoiding the human threat,
as reduced numbers of aggressive postures and increased

20 numbers of jumps to the front of the cage to confront
the human threat (Fig. 10). Again, as in the mouse,
anxiogenesis followed the withdrawal of treatment of
marmosets with nicotine. In the marmoset this was seen
as reduced time spent on the cage front confronting the

25 observer, increased time in the nest box avoiding the
observer and increased numbers of aggressive postures

(Fig. 10). These effects of withdrawal from nicotine were all significantly antagonised by AGN 2979 at a dose of 0.01 mg/kg s.c. Indeed, this treatment not only antagonised the anxiogenesis of nicotine

05 withdrawal but reversed this to anxiolysis seen as reduced time spent in the nest box, reduced numbers of aggressive postures, and increased numbers of jumps to and from the cage front to confront the human threat (Fig. 10).
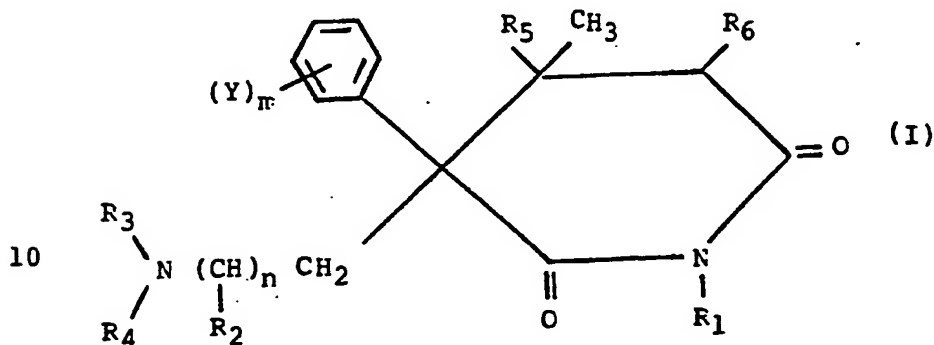
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CLAIMS

1. The use in the manufacture of a medicament for the treatment of anxiogenesis associated with addictive drug withdrawal of a compound of the following Formula

05 I.

wherein:

R_1 represents hydrogen or C_1-C_4 alkyl;

n is 1 or 2;

15   R_2 represents hydrogen or methyl, provided that one R_2 is hydrogen when n is 2;
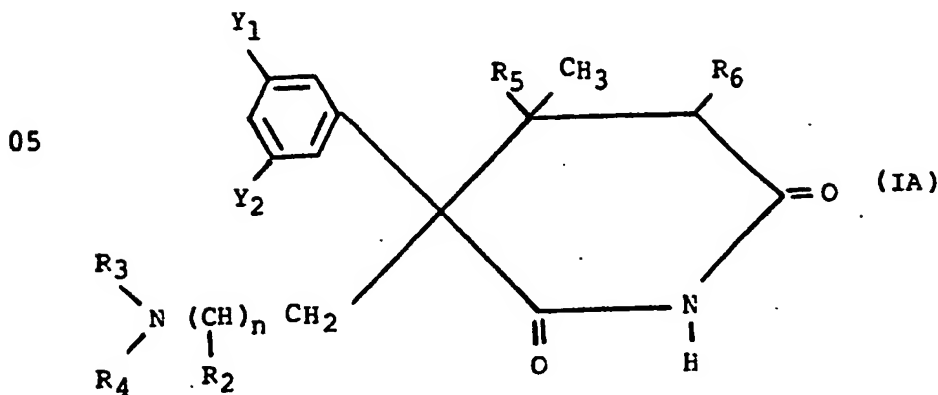
R_3 represents hydrogen or C_1-C_2 alkyl;

R_4 represents C_1-C_2 alkyl;

R_5 and R_6 independently represent hydrogen or

20 methyl;

m is 0 to 3; and

each Y is in a meta or para position and independently represents hydroxy, C_1-C_2 alkoxy, C_1-C_2 alkyl, C_1-C_2 hydroxyalkyl, halogen, or

25 trifluoromethyl, provided that hydroxy and alkoxy are not in the para position,

or a pharmacologically acceptable salt thereof.

2. A use as claimed in Claim 1, wherein the compound has the following Formula IA.

(IA)

wherein:

$\underline{n}$ is 1 or 2;

R_2 represents hydrogen or methyl, provided that one R_2 is hydrogen when $\underline{n}$ is 2;

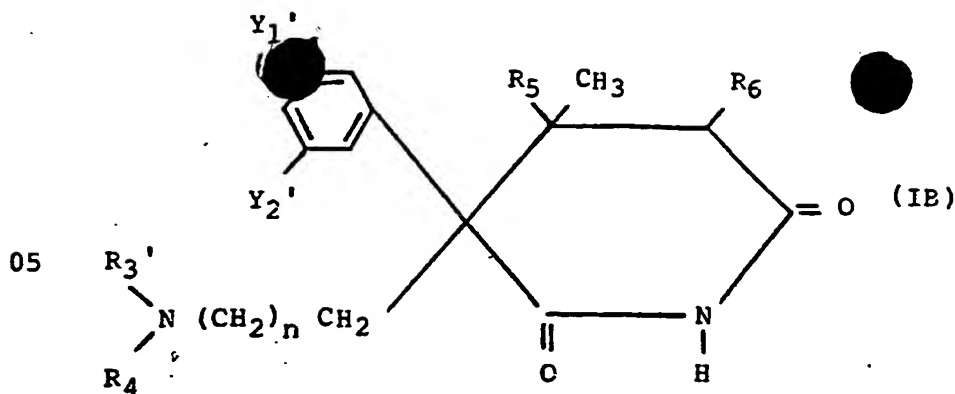R_3 represents hydrogen or C_1-C_2 alkyl;

R_4 represents C_1-C_2 alkyl;

R_5 and R_6 independently represent hydrogen or methyl; and

Y_1 and Y_2 independently represent hydrogen, hydroxy or C_1-C_2 alkoxy,

or a pharmacologically acceptable salt thereof.

3. A use as claimed in Claim 2, wherein the compound has the following Formula IB.

(IB)

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wherein:

n is 1 or 2;

10   R_3' and R_4 independently represent C_1-C_2 alkyl;

R_5 and R_6 independently represent hydrogen or methyl;

Y_1' represents hydroxy or C_1-C_2 alkoxy; and

15   Y_2' represents hydrogen, hydroxy or C_1-C_2 alkoxy,

or a pharmacologically acceptable salt thereof.

4.   A use as claimed in Claim 3, wherein Y_1' represents hydroxy or methoxy and Y_2' represents

20   hydrogen, hydroxy or methoxy.

5.   A use as claimed in Claim 3 or Claim 4, wherein Y_2' represents hydrogen.

6.   A use as claimed in any one of the preceding claims, wherein R_3 and R_4 both represent methyl.

25   7.   A use as claimed in any one of the preceding claims, wherein n is 2.

8.   A use as claimed in Claim 5, wherein Y_1'
represents hydroxy or methoxy, R_3 and R_4 both
represent methyl and $\underline{n}$ is 2.

9.   A use as claimed in any one of the preceding
claims, wherein R_5 represents methyl and R_6
represents hydrogen.

10.   A use as claimed in Claim 3, wherein the compound
is 3-(3'-methoxyphenyl)-3-(3"-N,N-dimethylaminopropyl)
-4,4-dimethyl-2,6-dixopiperidine.

11.   A use as claimed in Claim 10, wherein the compound
is the minus isomer.

12.   A use as claimed in Claim 3, wherein the compound
is 3-(3'hydroxyphenyl)-3-(3"-N,N-dimethylaminopropyl)
-4,4-dimethyl-2,6-dioxopiperidine.

13.   A use as claimed in any one of the preceding
claims, wherein the medicament is in unit dosage form
and contains 10^{-6} to 500 mg of the said compound of
Formula I.

14.   A use as claimed in any one of the preceding
claims, wherein the medicament is in unit dosage form
and contains 10^{-4} to 10^2 mg of the said compound
of Formula 1.

15.   A use as claimed in any one of the preceding
claims, wherein the medicament is in unit dosage form
and contains 10^{-3} to 10^{-1} mg of the said
compound of Formula 1.

16. A use as claimed in any one of the preceding claims, wherein the said addictive drug is alcohol.

17. A use as claimed in any one of Claims to 15, wherein the said addictive drug is nicotine.

05 18. A use as claimed in any one of Claims 1 to 15, wherein the said addictive drug is cocaine.

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